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Methods and Devices for Holding a Composition

Technical Field

The present invention relates to techniques and devices for packaging, or holding, compositions, and in particular, compositions containing an active agent.

Background Art

In manufacturing pharmaceuticals, cosmetics, food supplements as well as other products to induce some type of effect, an important consideration is how the quantities, or specific doses, of a composition are distributed to the consumer. Techniques of manufacturing the composition should be integrated with methods and devices for holding and/or packaging the composition; this may allow advantages such as streamlining production labor and decreased manufacturing costs. In the particular instance where the composition is embodied with an active agent-containing film, the film may be relatively sensitive, fragile, and easily deformable or damaged. Thus, integrating manufacturing techniques with design considerations for packaging and holding compositions may have the added advantages enhancing product stability and quality. Simultaneously, the risk of product deterioration may be decreased by minimizing exposure of the product to the environment (e.g. light, air, heat, moisture, etc.), isolating the product from contact with people, and facilitating product handling (e.g. preventing the stacking of films that may adhere to one another).

Summary of the Invention

One embodiment of the invention is directed toward a device for holding an active agent-containing composition. The device includes a support substrate; a pattern of adhesive in contact with one side of the support substrate; and an array of discrete film segments removably attached to the support substrate by contact with the adhesive, each film segment including the active agent-containing composition. The side of the support substrate facing the film segments, the array of film segments, and the pattern of adhesive may be sterile. The adhesive may be substantially inert to the film segments, and the

pattern of adhesive may be parallel lines. The device may also be stored in a separate container. The support substrate used in embodiments of the invention may be transparent. Each discrete film segment may contain a uniform quantity of the active agent.

Another embodiment of the invention is directed toward a device for holding an active agent-containing composition that includes a support substrate; an array of discrete film segments removably attached to one side of the support substrate, each film segment including the active agent; and a sealing material, the material covering the array of discrete film segments, a surface of the material heat sealed to the one side of the support substrate at locations surrounding at least one discrete film segment. Elements of the embodiment may be sterile. The surface of the sealing material may be heat sealed to the one side of the support substrate at locations surrounding each discrete film segment. The sealing material may be transparent or tear resistant. A portion of the surface of the sealing material may include a non stick coating to reduce adhesion between the film segments and the sealing material. The array of discrete film segments may be a dried polymer gel. Support substrates may be made of paper or a plastic sheet, and may be transparent. One side of the support substrate may include a coat of polyethylene that is optionally glossy or unexposed to Corona treatment. The sealing material may include a polyester sheet double-side coated with polyethylene (which may be ultra-dimensional stable), the surface of the polyester sheet heat sealed to the a side of the support substrate that is glossy. The corners of the support substrate may be detached from the sealing material.

In a related embodiment of the invention, the device for holding a composition includes a sealing material covering the array of discrete dosage units, a surface of the sealing material reattachably adhering to the one side of the support substrate by a pressure sensitive adhesive. The discrete dosage units may be an array of discrete film segments. A surface of the sealing material may be reattachably adhered to the one side of the support substrate such that at least one discrete dosage unit is surrounded by a reattachably adhered contact area between the sealing material and the support substrate.

In another embodiment of the invention, a device for holding a composition includes a support substrate; an array of dosage units contacting one side of the support substrate, each dosage unit including the composition; and a surface of a sealing material covering the array of dosage units. At least one selected portion of the surface of the sealing material includes a non stick coating where the sealing material contacts the

dosage units. The non stick coating may include either a fluorochemical or silicon-based compound. The surface of the sealing material may be attached to the support substrate, the non stick coating not being present at a location where the sealing material is attached to the support substrate. The array of dosage units may be an array of discrete film segments attached to the support substrate. The non stick coating on a surface of the sealing material may be on a plurality of locations corresponding to locations where the sealing material contacts each dosage unit, or may be on one continuous area. Optionally, the array of dosage units are attached to the support substrate by interposed adhesive.

Some embodiments of the invention may be directed toward a device for holding an active agent-containing composition that includes a support substrate; and a dried solution layer removably attached to the support substrate, the dried solution layer having the active agent-containing composition. The dried solution layer may be configured to deliver the active agent-containing composition to a patient by direct contact of the dried solution layer with the patient. The dried solution layer may also include a colorant to visually distinguish the dried solution layer from the support substrate.

Other embodiments of the invention refer to methods of creating the devices in previously described embodiments of the invention.

In another embodiment of the invention, a method for holding an active agent-containing composition includes providing a substrate; forming blister cavities in the substrate; covering the substrate with a film including the active agent-containing composition; displacing film segments into each blister cavity; removing the film unassociated with the segments; superposing a sealing material, the sealing material covering the segments of film and in contact with the substrate; and attaching the sealing material at a plurality of locations where the sealing material and substrate are in contact. The formation of the plurality of blister cavities and the displacing the film may occur substantially simultaneously. The displacing of film segments may include punching the film to displace the film segments into the blister cavities. The sealing material may be attached to the substrate using heat sealing, or by applying pressure at locations where a pressure sensitive adhesive is sandwiched between the sealing material and the substrate. The sealing material may be lacquered aluminum foil. Each segment of film may include a uniform quantity of the active agent.

An alternate method of holding an active agent-containing composition, in accord with an embodiment of the invention, includes providing a substrate with a plurality of

blister cavities; providing quantities of the active agent, each quantity contained in one of the plurality of blister cavities; superposing a sealing material, the material covering the quantities of the active agent-containing composition and in contact with the substrate; and attaching the sealing material at a plurality of locations where the sealing material and substrate are in contact. The sealing material may be attached to the substrate using heat sealing, or by applying pressure at locations where a pressure sensitive adhesive is sandwiched between the sealing material and the substrate.

In another embodiment of the invention, a method of applying a composition in a dosage unit to a dermal surface of a patient includes providing a dosage unit having the composition on a side of a final substrate that is larger in area than the dosage unit; holding the final substrate without touching the dosage unit; bringing the final substrate toward the dermal surface to bring the dosage unit into contact with the dermal surface; and pressing against the final substrate to apply the composition to the dermal surface. The method may also include one or more of moistening the dermal surface before the step of bringing the final substrate toward the dermal surface, and rubbing the final substrate to facilitate application of the composition to the dermal surface. When the dosage unit is a film segment, providing the dosage unit may include providing a dried solution forming a film on an intermediate substrate; removing the film from the intermediate substrate; forming a film segment from the film; and attaching the film segment to the final substrate. Providing the dosage unit may also include providing a substrate having a plurality of dosage units, and separating the substrate into a plurality of final substrates, each final substrate having at least one dosage unit. Alternatively, providing the dosage unit may include providing a plurality of final substrates, each final substrate having at least one dosage unit, each of the plurality of final substrates attached to at least one other final substrate. Optionally, providing the plurality of final substrates may include providing a substrate having a plurality of dosage units attached thereto; and perforating the substrate to form the plurality of final substrates.

In another embodiment of the invention, a method for holding an active agent-containing composition includes intermittently applying a solution containing the active agent to a substrate; and drying the intermittently applied solution to form film segments. Applying the solution may include at least one of spraying, printing, and casting the solution intermittently. When printing is utilized, the printing may be performed on a fabric, or by a gavure-type process. The film segments may be configured to deliver the active agent-containing composition to a patient by directly contacting the film segments

with the patient.

Various embodiments of the invention that include an active agent-containing composition may be utilized in an application that includes at least one of therapeutics, cosmetics, food supplements, wound healings, herbals, botanicals, aromatherapy, veterinary applications, agrochemicals, and cleansing applications.

Brief Description of the Drawings

The foregoing features of the invention will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

Figures 1A and 1B are a plan view and side view, respectively, of a device for holding active agent-containing compositions, in accordance with an embodiment of the invention, whereby film segments are attached onto a substrate by means of a pattern of adhesive.

Figures 2A – 2C are a series of side views illustrating the steps for making a device for holding film segments to a substrate material without the use of an adhesive, covered by a sealing material, embodiment.

Figures 3A – 3C is a series of schematic side views of the steps for making a device for holding active agent-containing compositions in a blister cavity-formed substrate attached to a sealing material embodiment.

Figure 4A depicts a side view of dosage units that are sandwiched between a support substrate and a sealing material that are attached by a cold seal process around the edges of the support substrate and sealing material, in accordance with an embodiment of the invention.

Figure 4B depicts a side view of dosage units that are sandwiched between a support substrate and a sealing material that are attached by a cold seal process at locations around each dosage unit, in accordance with an embodiment of the invention.

Figure 4C depicts a top view of dosage units that are surrounded by a pattern of adhesive that do not attach the corners of a support substrate, according to an embodiment of the invention.

Figure 4D depicts a top view of dosage units that are sandwiched between a support substrate and a sealing material, the sealing material irreversibly attached to an edge of the support substrate to form a reattachable flap, in accord with an embodiment of the invention.

Figures 5A and 5B present top views of embodiments of the invention that utilize a subdivided substrate with perforations, each subdivision containing a film segment and attached to the other subdivisions.

Figures 6A and 6B present top views of embodiments of the invention that utilize a non-stick coating applied to a sealing material to reduce adhesion with dosage units.

Detailed Description of Specific Embodiments

The embodiments described herein refer to methods and devices for holding compositions, including compositions containing active agents. The methods and devices may be employed to hold a plurality of dosage units, such as, for example, film segments, having an active agent-containing composition. The film segments may be formed from a film that includes the composition and may be configured in any desired shape and size.

For some embodiments described herein, film segments **115, 215, 315, 415, 515** may be composed from a film of dried polymer solution or dried polymer gel, either of which may also be hydrophilic in nature before drying occurs. The polymer gel or polymer solution may be formulated with a level of viscosity sufficient to allow the gel or solution to hold a specific configuration while drying occurs. The drying time depends upon a variety of factors that may include the type of solvents used, their concentration, the nature and concentration of the other constituents, the film thickness, the sensitivity of active components to high temperature, the air mass convected over the gel or solution, and the speed of film formation. For example, with heat sensitive materials, relatively low temperatures are preferred, requiring longer drying periods. Some embodiments may require a drying time of several minutes.

Polymers that may be utilized in the film segments **115, 215, 315, 415, 515** and the film **110, 210, 310**, include, for example, polyurethane, polyvinyl pyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC). A variety of materials including cellulose, starch and their derivatives, proteins, gelatins, etc may also be used. Other polymers include polymers of natural origin. One such embodiment is a plant prolamine, an example being gliadin, combined with other additives of natural origin; such additives may include a polar lipid, such as a ceramide. Each film segment **115, 215, 315, 415, 515** contains some amount of the composition to be delivered. A solvent, preferably ethanol when PVP or HPMC is used, is added to the polymer to make the solution.

The composition utilized in a dosage unit may belong to any category (e.g., compositions that are absorbed or applied to a patient by direct contact of a dosage unit with a patient). Some embodiments are preferably drawn to compositions with one or more active agents. An active agent may have a therapeutic effect (e.g., a pharmaceutical agent) or may have activity in other applications such as cosmetics, food supplements, wound healings, herbals, botanicals, aromatherapy, veterinary applications, agrochemicals (e.g., pesticides), cleansing applications (e.g., disinfectants), and other agents, in general. The active agent may be directed toward oral or topical application, such as epidermal, transdermal, or transmucosal (e.g., respiratory tract, oral cavity, vagina, penile surface, etc). The amount of active agent may be the same in each dosage unit and may also constitute a particular dosage of the active agent. Beyond active agents, compositions may also include thickeners, preservatives, colorants, microencapsulants, and other components that may alter the delivery or nature of an active agent.

Embodiments of the dried polymer film segments have thicknesses of 0.03, 0.05, and 0.06 millimeters, each segment having a surface area varying between 0.8 and 3.0 square centimeters. The film may also contain additional components that alter particular physical and chemical properties. For example, a film may include a plasticizer and an antioxidant.

In a specific example, dried polymer film segments include an active agent for treating erectile dysfunction, a polymer, a plasticizer, and an antioxidant. The dried film segments are circularly shaped with a surface area of 2.0 cm^2 and a thickness of 0.05 mm.

Though some embodiments described herein refer specifically to holding film segments with an active agent, these embodiments may also be used to hold other carriers with the active agent including various types of transdermal, epidermal, or transmucosal delivery systems (e.g. patches, tablets, capsules, and pills).

In some instances, sterilization of the device holding a composition helps preserve the composition in a particular state before their use. Thus alternatives to the embodiments described herein include application of methods and techniques known in the art to sterilize compositions, film segments, substrates, adhesives, sealing materials, and other materials. Examples of suitable sterilization techniques include gamma-irradiation and electron beam exposure.

Referring to Figure 1, a support substrate **100** is shown holding a plurality of film segments **115** each having an amount of the active agent. The film segments **115** are

removably attached to the support substrate **100** by an adhesive **140**, allowing the film segments **115** to be separated from the support substrate **100** by a user without damaging the segments **115**.

The support substrate **100** may be composed of any type of material that allows the film segments **115** to be removably attached to the support substrate **100** with an appropriate adhesive **140**. Preferred substrate materials include polyester, polystyrene, high density polyethylene, substrates treated with or made with a fluorochemical (e.g., Teflon®), paper, super-calendered (smoothed) paper, and polyurethane films. Laminates of the aformentioned materials may also be utilized. The support substrate **100** may be a release liner for the film segments **115**. In addition, the support substrate **100** may be transparent, allowing a person to view the film segments **115** through the support substrate **100**.

Selection of the adhesive is based in part upon the compatibility of the adhesive with one or more components of the formulation. Inertness of the adhesive is generally preferred. For example, salicylic acid containing formulations have been shown to interact chemically and are, therefore, incompatible with adhesives containing free hydroxyl and/or carboxyl groups. Combinations of salicylic acid and adhesives with free hydroxyl and/or carboxyl groups may suffer from one or more of stability problems, deformation of the formulation or adhesive layer; the problems may lead to the deterioration of the product's properties (e.g., activity and physical appearance). Thus, these combinations, and contact with such, are preferably avoided. With regard to tacking properties, the adhesive may impart a peeling load/width within a range of 5-50 gf/inch, as measured by a 180° peel test, to attach the film segments to the support substrate, while allowing the segments to be removed from the substrate without damage. Examples of possible adhesives for use with the embodiment include, but are not limited to, Duro-Tak® (produced by National Starch), Gelva® (produced by Solutia), and other commercially available polyacrylic adhesives.

The adhesive **140** may be applied in a particular pattern on the support substrate **100**. For example, the adhesive **140** may constitute sets of closely spaced parallel lines **145** that allow the film segments **115** to be arranged in the pattern of a rectangular matrix, as depicted in Figure 1A. In a particular embodiment, the adhesive is applied in three pairs of adhesive lines, each line being approximately 80 millimeters long, 2 millimeters wide, and 0.02 millimeters thick. The adhesive **140** allows the film segments **115** to be removably attached to the support substrate **100**. In addition, the adhesive **140** is chosen

such that it does not adversely affect the chemical or physical nature of the active agent or film segments **115**.

Referring to Figures 1A and 1B, one method for making the device, in accord with embodiments of the invention, includes the steps of: (a) providing a final support substrate **100** with a pattern **145** of adhesive **140** in contact with a side of the support substrate **100**; (b) removably attaching a film **110** with the active agent to the final support substrate **100** through contact with the pattern of adhesive **145** as shown in Figure 1B; and (c) segmenting the film **110** to form an array of film segments **115** attached to the final support substrate **100** through contact with the adhesive **140**. In a particular embodiment of the method, the step of removably attaching the film **110** to the final support substrate **100** includes providing the film **110** with the active agent removably attached to an initial support substrate; bringing the film **110** in contact with the pattern of adhesive **140**; and delaminating the initial support substrate from the film **110**, leaving the film **110** attached to the final support substrate **100**.

In the particular method described above, the initial support substrate may be composed of any material that has the property of adhering to the film **110** more weakly than the final support substrate **100** adheres to the film **110**. The film's adherence to the initial support substrate may be an intrinsic property of the two surfaces, or may be facilitated by the use of an adhesive. Possible initial support substrates include release liners. Release liners for the initial support substrate may include a side, which contacts the film **110**, being treated with either a silicon-based compound or a fluorochemical such as Teflon®. For example, in the case of a silicon-based compound, a polyethylene terephthalate substrate is coated with a mixture containing a polysiloxane with vinyl-functional side chains or hydroxyl-functional side chains; a crosslinker (e.g., a polysiloxane with Si-H functionality); a platinum or tin complex as a catalyst; and optionally solvent and/or additives. The mixture is heated to react the components to form a network of polysiloxanes. Any remaining solvent is subsequently removed. The resulting coating is a thin silicone-like layer.

Segmenting the film **110** into an array of film segments **115** may include one or more processes, non-exhaustive examples being cutting and removing of the film **110**. In a particular segmenting process, kiss-cutting of the film **110** is performed. Kiss-cutting involves making cuts that penetrate the film **110**, while not penetrating the support substrate **100**. The kiss-cutting is followed by removal of a portion of the film from the support substrate **100**, leaving discrete film segments **115** that adhere to the support

substrate **100** by contact with adhesive **140**, as depicted in Figure 1A. The remaining film that is not utilized as film segments **115** may be discarded or recycled to formulate more film.

The steps of the method may be performed to produce a continuous product. In such an instance, an additional step of cutting the final support substrate **100** with attached film segments **115** into discrete sets is included. Machinery, such as the Allied Gear and Machine Co.'s Flexomaster IB press, may be utilized to perform one or more steps of the method continuously. In an embodiment of the method, the step of segmenting the film may be performed by the Flexomaster IB press. In this embodiment, the film **110**, support substrate **100**, and adhesive **140** are provided as a continuous laminate that is rolled up. The laminate is unrolled by the machine and kiss-cut by a first cutting tool, and perforated and scored by a second cutting tool. The machine may also be configured to perform some preprocessing steps on the laminate, such as printing, before kiss cutting occurs. The cutting tools are configured to accommodate the specific film thickness and support substrate utilized. Film **110** that is not utilized in the film segments, scrap, is delaminated from the original laminate and wound up in a roll. The remaining laminate, including film segments **115** attached to a support substrate **100** through contact with adhesive **140**, is rewound on a roll for further processing.

One or more sets of the film segments **115** attached to the final support substrate **100** may be packaged in a pouch, or other container, to protect the assembly from potential hazards that may include physical damage, contamination, light exposure, or other environmental elements.

Another embodiment of a device for holding an active agent-containing composition is shown in Figure 2C. In this embodiment, film segments **215** are removably attached to a support substrate **200** without the use of an adhesive; adhesion of the film segments **215** to the support substrate **200** is due to the nature of the interaction between the segments **215** and the support substrate **200**. Minor self-adhesive properties of the film segments, substrate surface roughness (surface irregularities created by a particular treatment method), and temporarily induced electrostatic charges provide some examples of mechanisms that result in adhesion between the segments **215** and support substrate **200**. A sealing material **220** covers the film segments **215** so that the segments are protected in a sandwich between the support substrate **200** and the sealing material **220**. The sealing material **220** is heat sealed to the support substrate **200**, to enclose the film segments in a sealed package. The film segments **215** are protected from potential

hazards that may include physical damage, contamination, light exposure, and other environmental conditions.

The support substrate **200** may be composed of any type of material that allows the film segments **215** to be removably attached to the support substrate **200** and does not cause adverse physical or chemical changes to the nature of the active agent or film segments **215**. Examples of acceptable support substrate materials include paper or plastic sheets. The support substrate **200** may be a release liner. In a particular embodiment, the support substrate **200** is composed of a polyethylene-coated paper. The side of the polyethylene-coated paper that adheres to the film segments **215** is glossy, and not Corona treated, i.e. the side has a smooth, reflective surface that has not been treated to introduce any surface irregularities. This insures that adhesion of the film segments **215** to the support substrate **200** is not so strong as to prevent the segments **215** from being removed without damage. The support substrate **200** may also be made of a transparent material, allowing persons to view the film segments through the support substrate **200**.

One embodiment of a sealing material **220** utilizes a polyester sheet double side coated with polyethylene, the surface of the film that contacts the support substrate **200** being glossy. In particular, this embodiment of the sealing material **220** may be configured to be especially stable. Examples of the embodiment include the ultra-dimensional stable polyester films produced by Loparex. The films are polyester films coated with a layer of low-density polyethylene on each side. These films do not lose moisture when heated, and, therefore, do not change their dimensions upon heating, i.e., they do not tend to curl, and are thus considered very stable liners.

The sealing material **220** may be composed of any material that may be heat sealed to the support substrate **200**. The sealing material **220** may be transparent, allowing the film segments **215** to be seen through the sealing material **220**. The sealing material **220** may also be chosen to be tear resistant.

The sealing material **220** may be heat sealed to the support substrate **200** such that each film segment **215** is isolated from the other film segments **215** as shown in Figure 2C. The sealing material may also be intentionally unattached to the support substrate in particular locations, e.g. the corners of the sealing material, to allow ease of separation of the sealing material from the support substrate by a user.

As shown in Figures 2A – 2D, a method for making the device includes the steps of applying a film **210** having the active agent to a side of a support substrate **200**;

segmenting the film **210** into film segments **215**; covering the film segments **215** with a sealing material **220**; and heat sealing the sealing material **220** to the support substrate **200**. The film segments **215** are attached to the support substrate **200**, but may be removed therefrom without damage to the film segments **215**. In particular, the method may include using a polymer gel or polymer solution to make the film **210**, and include the step of drying the film **210** after the film **210** is applied to a support substrate **200**.

The step of segmenting the film **210** may include kiss-cutting the film **210** and removing the film portions that are not utilized as film segments **215** on the support substrate **200**. Excess film may either be discarded or recycled to formulate more film. A continuous process may be employed to carry out the steps of this method; in such a case, the method further includes a step of cutting the attached support substrate **200** and sealing material **220** holding a plurality of film segments **215** to create sets of the held film segments **215**.

In a preferred embodiment of the method, a coating machine applies the polymer solution or polymer gel to the support substrate, forming a laminate sheet. The solution or gel is dried, and the laminate wound up into a roll. The Allied Gear and Machine Co.'s Flexomaster IB press, that was described earlier to create the embodiment in Figure 1, can be utilized with the roll created by the coating machine to kiss-cut and delaminate the scrap material not being packaged.

Referring to Figures 3A – 3C, an alternate method of producing a device for holding film segments with an active agent- containing composition is described. Discrete film segments **315** including the active agent are deposited into individual blister cavities **305** of a substrate material **300**. The film segments **315** may be formed from an original film **310** containing the active agent. A sealing material **320** is placed over the blister cavities **305** containing the film segments **315** and attached to the substrate material **300** to contain the film segments **315**. The film segments **315** may be free from attachment while contained within the blister cavity **305** covered by the sealing material **320**.

The substrate material **300** may be any material to which blister cavities **305** may be formed. Blister cavities **305** are stable impressions in the substrate material **300** that are sized to contain individual film segments **315**, as depicted in Figures 3B and 3C. When the substrate **300** is oriented such that the blister cavities **305** are in a concave downward orientation, as depicted in Figures 3A – 3C, individual film segments **315** may be contained within each blister cavity **305**, with an open top surface as depicted in

Figure 3B. Examples of suitable materials for the substrate material **300** include, but are not limited to, polyvinyl chloride, a combination of polyvinyl chloride and polyvinylidene chloride, and aluminum.

The formation of blister cavities **305** in the substrate material **300** and depositing of film segments **315** into the blister cavities **305** may be performed using various techniques. In one technique, film segments **315** are provided on a blister cavity-free substrate material. The film segments **315** may be formed and provided on the substrate material **300** utilizing the methods described earlier to form the embodiments depicted by Figure 2. The film segments **315** may be held in place on the substrate material **300** by electrostatic charges. Next, a machine forms blister cavities **305** in the substrate material **300** at positions where film segments **315** are located. The blister cavities **305** may be formed by any technique known to those in the art. In one embodiment, the blister cavities **305** are formed by moving the substrate **300** over an appropriately sized and shaped orifice in a surface of a machine. The substrate material **300** is drawn into the orifice, deforming permanently into a shape confined by the orifice and creating the blister cavity **305**. The process of deforming the substrate material **300** may utilize heat or mechanical force. For example, a vacuum may be used to provide suction to a surface of the substrate to deform the substrate locally to form a blister cavity. In another example, a punch may be used to contact the substrate material surface and deform it locally into a blister cavity. Optionally, the portion of the substrate to be deformed may be heated before deformation takes place to facilitate blister cavity formation. Since each blister cavity **305** is formed adjacent to a film segment **315**, upon cavity formation the segment **315** is simultaneously deposited into the cavity **305**.

In another technique, a film **310** is placed over a blister cavity-free substrate material. A machine forms blister cavities **305** in the substrate material while also displacing a film segment **315** from the film **310** into each blister cavity **305**. In one embodiment, the blister cavities **305** are formed by drawing the substrate material **300** into an orifice, as discussed above. At approximately the same time, film segments **305** are displaced from the film **310** by impinging a punch **330** against the film **310** on a side opposite the substrate material **300**. The shape of the punch may be chosen to create a desired film segment size. The punch **330** may have a surface that impinges upon the film **310** that is flat or curved. The punch contact surface may also have the shape of an annular ring or frame of any desired shape or size. The punch **330** preferably has edges that are sharp enough to cut the film **310**. The punch **330** forms film segments **315** that

are deposited into the blister cavities **305**. The punch **330** is subsequently withdrawn. Alternatively, one or more punches may be used to preform blister cavities in a substrate, followed by the punching of a film disposed over the substrate to deposit segments into the blister cavities.

In a third technique, a substrate material **300** with preformed blister cavities **305** is provided. The blister cavities **305** may be formed by any technique known in the art including the particular technique described above. A film **310** with the active agent is positioned over the substrate material **300** on a side of the substrate material **300** in which the blister cavities **305** protrude away from the film **310**, as depicted in Figure 3A. A machine impinges the film **310** with a punch **330** on a side opposite the substrate material **300** in positions over the blister cavities **305**. The punch contact creates a film segment **315** which is separated from the film **310** and deposited into the blister cavity **305**.

Subsequent to the depositing of film segments into the blister cavities, a sealing material is used to contain the film segments within the cavities. The sealing material **320** may be any material that may be attached to the substrate material **300**. In a particular embodiment, the sealing material **320** is heat sealable to the substrate material **300**. One example of a sealing material **320** is lacquered aluminum foil. Other properties of the sealing material **320** that may be desirable include transparency and tear resistance..

The sealing material **320** is placed over openings of the blister cavities **305** that contain the film segments **315**. Portions of the sealing material **320** are in contact with the substrate material **300**. In a particular configuration, the sealing material **320** contacts the portions of the substrate **300** that do not constitute a blister cavity **305**. Locations of contact between the sealing material **320** and substrate material **300** may be heat sealed, thus containing the film segments **315** within the blister cavities **305**. The heat sealing may take place around each blister cavity to ensure isolation of each film segment. The corners of the substrate or sealing material may not be heat sealed to allow easier separation of the layers when access to the film segments is desired by a consumer.

The method may be practiced in a continuous process that forms a continuous substrate with blister cavities **305**, film segments **315**, and sealing material **320**. A plurality of blister cavities **305** and/or film segments **315** may be formed in a batch process that is carried out successively. The continuous method would include the step of cutting the substrate **300** to provide discrete sets of the film segments **315**.

In an alternative to this blister cavity packaging method, the film segments are preformed and deposited into preformed blister cavities in a substrate material. In this

embodiment, the method and device are not necessarily limited to the packaging of film segments but may include packaging of active agents in other forms including patches, tablets, and pills.

Dosage units **415** may be held between a support substrate **400** and a sealing material **420**, the support substrate **400** attached to the sealing material **420** by a cold seal process, in an embodiment of the invention as depicted in Figures 4A – 4D. The cold seal process utilizes a pressure sensitive adhesive **440, 445, 446** that reattachably adheres the sealing material **420** to the support substrate **400**, i.e., the sealing material **420** may be separated from the support substrate **400** and subsequently reattached by applying pressure between the two layers **400, 420** at the positions where adhesive **440, 445, 446** is applied. The adhesive **440, 445, 446** may be applied to either layer **400, 420** or both. The adhesive **440, 445, 446** may also have the property of only adhering to itself or a surface with a particular chemical nature. In a particular embodiment, the substrate is composed of a multilaminate of paper/polymer/foil/polymer, such as Type 7340 (Phoenix Health Care Products, LLC, Milwaukee, WI), and the adhesive is a compounded natural rubber latex, such as PHX 3/03AX, PHC 3/03AX, or CSC 3/03AX (Phoenix Health Care Products, LLC, Milwaukee, WI).

As shown in Figures 4A and 4B, the pattern of applied adhesive may surround one or more dosage units, and may be in any pattern that is advantageous. As shown in Figure 4C for example, the adhesive pattern **445** is directed away from the corners of the support substrate **400** to facilitate separation of the support substrate **400** and sealing material **420**. Alternatively, a portion of the support substrate and sealing material may be permanently bonded, while another portion of the support substrate and sealing material are reattachably adhered. For example, as depicted in Figure 4D, the support substrate **400** and sealing material **420** are permanently bonded **447** at an edge to form a reattachable flap **425** with the sealing material, the adhesive pattern **446** serving to reattachably adhere the flap **425** to the support substrate **400**.

Use of a cold seal process may provide several advantages. A consumer may peel the sealing material from the support substrate to obtain one of the dosage units, and subsequently reattach the layers to keep other dosage units protected until use. Thus cold sealing may alleviate the costs associated with packaging individualized dosages. A cold-seal process may also avoid the risk of heat damage that may be sustained to a substrate, sealing material, or dosage unit if a heat sealing process is utilized, as well as need for specialized machinery.

The use of a cold seal process may be utilized with several of the aforementioned embodiments of the invention including when dosages are attached to the substrate, either by adhesive or self-adhesive nature of a dried film segment, or placed in a blister cavity configuration. Dosage units may be film segments, as described herein, or other carriers such as mini-tablets and suppositories containing active agents. Use of a cold seal process may also allow the use of radiation to sterilize embodiments of the invention without affecting the particular properties of the embodiment (e.g., adhesive bonding, active agents' potency, substrate material's optical or mechanical properties, sealing material's optical or mechanical properties, and others).

Film segments, carrying an active agent and attached to a support substrate, may be used to apply the active agent to a dermal surface of a patient in another embodiment of the invention. As shown in Figures 5A and 5B, a substrate **500** with film segments **515** distributed thereon may be divided into subdivisions. Each subdivision **560** may be attached to one film segment **515**, the side of the subdivision contacting the film segment having a surface area greater than the film segment. One film segment may hold a particular dosage of active agent. A film segment may then be placed in contact with a dermal surface to transfer the contacting agent. In particular, a patient may manipulate the film segment to contact a dermal surface by handling the subdivision and not contacting the film segment. Subsequently, upon transfer of the active agent, the subdivision may be disposed, again without contact with the agent by handling the subdivision only. Thus patient exposure to the contacting agent may be limited to only the dermal contact desired.

A film segment may include the use of a colorant that facilitates the visual distinction between a film segment and the support substrate or subdivision that the film segment to which the film segment is attached. Thus successful transfer of the film segment to a dermal surface may be more easily identified by the substantial absence of colorant on the support substrate or subdivision.

Agent transfer may be facilitated by applying pressure to the film through the subdivision. In addition or optionally, the dermal surface may be moistened with saliva, water, or some other liquid to promote agent transport. Transfer of the agent may include transfer of part, or the entire, film segment that contacts the dermal area.

Formation of the film segments that are attached to a support substrate may be performed in numerous manners. In one example, a solution containing the contacting agent may be applied to an intermediate support substrate. The applied solution is dried

to form a film. The dried film may be removed as a sheet from the intermediate support substrate, and separated into film segments (e.g., cutting the sheet). The film segments are attached to the support substrate (e.g., polyethylene or polypropylene) that is subsequently subdivided. This method can advantageously invoke use of most, if not all, of the film.

In another example, a solution containing the active agent-containing composition may be applied in an intermittent manner to the substrate that is subsequently subdivided. The intermittently applied solution is dried to form the film segments. Intermittent solution application may be by any known conventional method including solution casting, spraying, or printing (e.g., "silk-screen printing" or "gravure-type"). In the specific instance where silk-screen printing is utilized, types of substrates that may be utilized include non-woven material, fabrics, and polyesters that are optionally siliconised. The intermittent pattern of applied solution, and the amount of solution applied for forming each film segment, may vary as required for a particular application. For example, the segments may be shaped to conform to a particular application location such as the lips or eyes. Figures 5A and 5B show two possible layouts of solution application. Forming film segments in this manner saves resources by eliminating wasted film and the use of an intermediate substrate.

Dividing a substrate into a plurality of subdivisions may be performed in a number of manners. In one example, the substrate is cut into separate subdivisions that may be subsequently packaged. In another example, the substrate may be perforated **550** into subdivisions, the subdivisions still connected with each other as depicted in Figures 5A and 5B. The perforations allow a patient to subsequently separate the subdivisions for individual use. In a third example, a patient may simply tear, without preset guidance, the substrate to remove a film segment attached to the torn subdivision.

In embodiments of the invention that utilize a sealing material, the sealing material may have a selected portion of its surface that limits adhesion of the sealing material with the dosage units that may contact the sealing material. As shown in an embodiment of the invention shown in Figure 6A, a surface of a sealing material **620** in contact with a plurality of dosage units associated with a substrate is treated at a plurality of locations **670** with a non-stick coating. When the sealing material **620** is attached to a substrate at location **645**, the locations **670** correspond with areas where dosage units may contact the sealing material **620**. The coating **670** reduces the adhesion of the dosage units with the sealing material **620**, to help prevent the dosage units from being damaged

when the sealing material **620** and substrate are separated. Such an embodiment may be especially useful in situation where "cold flow" of adhesive, which attaches a dosage unit to a desired site, may cause undesirable adhesion between the substrate and sealing material at position close to a dosage unit, and/or adhesion between the dosage unit and the substrate and/or the sealing material, possibly damaging the dosage unit when the substrate and sealing material are separated.

Non-stick coatings that may be utilized include silicon-based coatings and fluorochemical-based coatings (e.g., Teflon®). Such coatings may be applied to the surface of the sealing material in any pattern (e.g., lines, islands, spots, etc.) that may be advantageous to preventing damage to the dosage units when the sealing material is separated from the substrate. In Figure 6A, the non-stick coating is applied at a plurality of discrete locations **670** corresponding to the contact points between the sealing material **620** with the dosage units. Alternatively, as shown in Figure 6B, the non-stick coating is applied to a large area **675** of the sealing material **620** surface that includes potential contact locations between the dosage units and sealing material **620**. In general, the non-stick coatings are applied to the sealing material in a manner to avoid contact with locations of the sealing material that are intended to bind the sealing material to the substrate (e.g., the edges **645** of the sealing material **620** shown in Figures 6A and 6B).

The aforementioned embodiments are intended to be merely exemplary; numerous variations and modifications will be apparent to those skilled in the art, including variations and modification that utilize one or more particular features from one or more various described embodiments. All such variations and modifications are intended to be within the scope of the present invention.